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TELEFAX

Date: February 23, 2006 **Total pages:** 15 w/cover sheet

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Our Docket No. YU 132
Your Docket No. **Client/Matter No: 078245-00045**

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MESSAGE:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter M. Glazer		
Serial No:	09/978,333	Art Unit:	1634
Filed:	October 15, 2001	Examiner:	Carla Myers
For:	*TRIPLE-HELIX FORMING OLIGONUCLEOTIDES FOR TARGETED MUTAGENESIS*		

Attachments:
Transmittal Form PTO/SB/21;
Fee Transmittal PTO/SB/17;
Reply Brief; and
Request for Oral Hearing

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PTO/SB/21 (09-04)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/978,333
Filing Date	October 15, 2001
First Named Inventor	Peter M. Glazer
Art Unit	1634
Examiner Name	Carla Myers
Attorney Docket Number	YU 132

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
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- [ ] CD, Number of CD(s) _____
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- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [✓] Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [✓] Other Enclosure(s) (please identify below):
  Request for Oral Hearing

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Pabst Patent Group LLP		
Signature			
Printed name	Patrea L. Pabst		
Date	February 23, 2006	Reg. No.	31,284

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Signature			
Typed or printed name	Ronna Berman	Date	February 23 2006

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Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 500

Complete if Known	
Application Number	09/978,333
Filing Date	October 15, 2001
First Named Inventor	Peter M. Glazer
Examiner Name	Carla Myers
Art Unit	1634
Attorney Docket No.	YU 132

METHOD OF PAYMENT (check all that apply)

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☑ Deposit Account Deposit Account Number: 50-3129 Deposit Account Name: Pabst Patent Group LLP

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
17 - 25 or HP =	x	0.00	= 0.00		

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
1 - 3 or HP =	0 x	0.00	= 0.00

HP = highest number of independent claims paid for, if greater than 3

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/ 50 =	(round up to a whole number)	x	=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: Request for Oral Hearing	$500.00

SUBMITTED BY

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Name (Print/Type)	Patrea L. Pabst		Date February 23 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Peter M. Glazer		
Serial No.:	09/978,333	Art Unit:	1634
Filed:	October 15, 2001	Examiner:	Carla Myers

For: *TRIPLE-HELIX FORMING OLIGONUCLEOTIDES FOR TARGETED MUTAGENESIS*

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REPLY BRIEF

Sir:

This is a Reply Brief to the Examiner's Answer mailed December 23, 2005, in the above-identified patent application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $500, the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues now present on appeal are:

(1) whether claims 7-12 and 15-25 are enabled as required by 35 U.S.C. § 112, first paragraph.

(2) whether claims 7-12 and 25 are novel as required by 35 U.S.C. § 102(b) over Chan, et al., *Journal of Biological Chemistry* 274:11541-11548 (1999) ("Chan").

Appellant appreciates the withdrawal by the Examiner of the rejection of claims 15-24 under 35 U.S.C. § 112, second paragraph, the rejection of claims 15-21 and 23-24 under 35 U.S.C. § 102(b) as anticipated by Chan and the rejection of claim 22 under 25 U.S.C. § 103(a) as being obvious in view of Chan.

(2) ARGUMENTS

Appellant affirms all of the arguments made in the Appeal Brief.

(i) Rejection under 35 U.S.C. § 112, first paragraph

To comply with 35 U.S.C. § 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). However, this is what the Examiner wants. The crux of the Examiner's argument is that the Examiner thinks that the claims are allegedly not enabled because the Appellant has not demonstrated therapeutic efficacy. However, the claims do not require therapeutic efficacy. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of

the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As set forth in *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables **any** mode of making and using the invention." These requirements have clearly been met by the Appellant.

Claims 7-12 are enabled

Independent claim 7 defines a method for targeted recombination of a nucleic acid molecule comprising the steps of: a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule with a K_d of less than or equal to 2×10^{-7}; and b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule. Nowhere in this claim or the dependent claims are limitations concerning therapeutic efficacy.

The components required by the claims include a single-stranded oligonucleotide that forms a triple-stranded nucleic acid molecule and a donor nucleic acid. Single-stranded oligonucleotides that form a triple-stranded nucleic acid molecule (or TFOs) are described in the specification at least at page 7 to page 11. TFOs were well known to one of skill in the art at the time of filing the present application (see at least page 2, lines 1-5). Furthermore, the specification spells out in detail that such oligonucleotides can be synthetic or isolated, are preferably 10 to 60 nucleotides in length and should have a low dissociation constant (K_d). Not

only does the specification describe suitable dissociation constants for TFOs (such as those required by the claims), the specification also describes methods for determining the dissociation constant of an oligonucleotide/target pair.

Donor nucleic acids are described in the specification at least at page 9, lines 11-28 and page 14, lines 8-25. The donor nucleic acid can be tethered or un-linked to the single stranded oligonucleotide as described in the specification at least at page 17, lines 19-26.

The claims define methods for targeted recombination of a nucleic acid molecule comprising administration of a TFO and a donor nucleic acid molecule. There is no dispute that the claims are enabled for *in vitro* and *ex vivo* methods. The Examiner's arguments focus on the fact that the claims are allegedly not enabled for *in vivo* methods. However, all that is required to practice the method as defined by the claims is (1) provision of a suitable TFO and donor nucleic acid and (2) injection of the TFO and donor nucleic acid. As described above and in the Appeal Brief, the specification enables one of skill in the art to make and use suitable TFO and donor nucleic acids. Therefore, all one of skill in the art must do to perform the methods defined by the claims *in vivo* is inject them. The Examiner has provided no evidence to support her arguments that the claims are not enabled. As discussed above, the Examiner is arguing that Appellant should demonstrate therapeutic efficacy. ***This is not the legal requirement when the claims do not require <u>therapeutic</u> efficacy.***

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In this case, it is clear that those skilled in the art engage in *in vivo* methods. Methods for

insertion of a homologous DNA sequence or DNA fragment *in vivo* and methods of targeting TFOs to a specific site in the genome were known to one of ordinary skill at the time of filing the present application. As described in detail in the Appeal Brief, one of ordinary skill in the art would expect that a TFO injected into an animal would result in site-directed mutagenesis as predicted by the *in vitro* data. Indeed this is exactly what Appellant demonstrates in Examples 6 and 7: injection of the TFO resulted in site-directed mutagenesis *in vivo* as predicted from the *in vitro* data. There has been no evidence provided by the examiner that the evidence in the specification would not be predictive of an oligonucleotide which further included a donor nucleic acid. The Examiner merely argues that the mutations are not sufficient for *therapeutic* efficacy. However, the evidence in the specification clearly demonstrates efficacy in a cell system which was predictive of the actual efficacy in animals. *There is no legal requirement for enablement of a certain amount of efficacy;* all that is required is that the specification (coupled with what is known in the art) provides one of ordinary skill with the ability to make and use the method defined by the claims without undue experimentation. This Appellant has done. Furthermore, Appellant has provided working examples for the oligonucleotides linked or unlinked to a donor nucleic acid using both cell-free and cell systems (see Examples 2-4 in the specification at pages 27-31). Absent some evidence otherwise, one skilled in the art would expect the oligonucleotides, linked or unlinked to a donor nucleic acid, to promote targeted recombination in animals as in the cell systems, based on the evidence in the specification. One of ordinary skill in the art would expect that injection of nucleic acid molecules as defined by the claims into an animal would result in distribution of the nucleic acid molecules to tissues and cell

nuclei, thereby resulting in targeted recombination of a donor nucleic acid into a target DNA sequence. Therefore, it would not require undue experimentation to practice the method for targeted recombination *in vivo* as defined by claims 7-12.

Claims 15-25 are enabled

Dependent claims 15-25 specify that the method of claim 7 is carried out to produce changes in the genome of an intact human or animal. As discussed in the Appeal Brief, studies have established that DNA molecules can be administered by i.p. or intravenous injections and will gain access to tissues and cell nuclei. As expected from these studies, Appellant demonstrated that chromosomal DNA throughout the somatic tissues of an animal can be targeted by nucleic acids, which is described in the specification at least at examples 6 and 7, pages 31-35. Since *in vivo* distribution of nucleic acids is achieved by injection of nucleic acids and all that is required to practice the method as defined by the claims is injection of a TFO linked or unlinked to a donor nucleic acid, it is clear that the quantity of experimentation required to practice the claimed method is minimal. It is also clear from the amount of guidance provided in the specification as discussed above that the amount of experimentation required to practice the claimed method is not undue.

(ii) Rejection Under 35 U.S.C. § 102

Chan

The Examiner has only maintained his rejection of claims 7-12 and 25 under 35 U.S.C. § 102(b) as anticipated by Chan. However, as discussed thoroughly in the Appeal Brief, Chan is not prior art as the present application is entitled to a priority date of 1995. The discussion below

refers to U.S. Patent No. 6,303,376 ("the '376 patent") and U.S. Patent No. 5,962,426 ("the '426 patent"). A discussion of the relationship between the '376 and '426 patents and the present application was provided in the appeal brief.

With respect to claims 7-12, the Examiner argues that the '376 and '426 patents do not support conception of (1) a K_d of less than or equal to 2×10^{-7}, (2) TFOs having a length between 10 and 60 nucleotides, and (3) a TFO that is tethered or untethered to a donor nucleic acid. With respect to claims 12 and 25, the Examiner argues that the '376 and '426 patents do not support a donor nucleic acid at least 30 nucleotides in length or between 10 and 40 nucleotides in length.

In response to Appellant's Appeal Brief, the Examiner argues that a claim as a whole is assigned an effective filing date rather than the subject matter within a claim being assigned individual effective filing dates. However, the Examiner lumps claims 7-12 together during her arguments and does not examine each claim individually. It should be noted that element (2) is only recited in claim 8. Moreover, element (2) is recited in claim 16, which is allowed.

It has been well established that a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Furthermore, "the meaning of equivalents is well understood in patent law, and an applicant need not describe in his specification the full range of equivalents of his invention" (citation omitted). *Noll*, 545 F.2d at 149-50, 191 USPQ at 727.

TFOs and methods of making and using TFOs were <u>well</u> known to one of skill in the art as described in the '376 patent at least at column 1, line 24 to column 2, line 10. The '376 patent

also discloses at least at column 4, lines 55-64 that the conditions under which a triple-stranded structure will form are standard assay conditions for *in vitro* mutagenesis and physiological conditions for *in vivo* mutagenesis. The '376 patent defines **exemplary** suitable dissociation constants (K_d) at least at column 5, lines 3-4, and at column 9, lines 25-56, and at Table 1. Specifically, Table 1 states that AG20 has a Kd of 3×10^{-7} and AG 30 has a Kd of 2×10^{-8}. These results in Table 1 demonstrate that TFOs with Kd's of 3×10^{-7} or less result in mutagenesis induced by triple helix formation. Since 2×10^{-7} is obviously less than 3×10^{-7}, dissociation constants of less than or equal to 2×10^{-7} are supported by the '376 patent. Furthermore, the '376 patent at least at column 5, lines 7-35, provide methods for determining a K_d of less than or equal to 2×10^{-7} for an oligonucleotide/target pair. Therefore, claims 7-12 and 25 are supported by the '326 and '476 patents.

The Examiner argues that the '376 and '426 patents do not support the concept of a TFO having a length between 10 and 60 nucleotides as defined by claim 8. As discussed above, TFOs were well known in the art and a patent should preferably omit what is well known in the art. The '376 and '426 patents discloses **exemplary** suitable TFOs of 7 to 40 nucleotides (see column 4, line 4 of the '376 patent) and TFOs of 10, 20, 30 and 57 nucleotides in length. This clearly demonstrates that the Appellant had conceived that TFOs of different lengths were suitable for use in the methods defined by the claims and demonstrates TFOs of between 10 to 60 nucleotides in length as defined in claim 8 is supported by the '376 and '426 patents.

The Examiner also alleges that the '376 and '426 patents do not support conception of a TFO that is tethered or untethered to a donor nucleic acid. Based on the level of knowledge in

the art, one of skill in the art would have recognized that a TFO and donor nucleic acid can be used in a tethered or untethered manner based on the disclosure of the '376 and '426 patents. At least at the paragraph spanning column 1 to column 2, the '376 patent discloses that TFOs are useful alone *or linked to reactive moieties*. The '376 patent at least at column 3, lines 49-56, describes methods for using TFOs to stimulate recombination of a DNA fragment into a target region. Furthermore, the '376 patent discloses at least at column 6, lines 40-58, that a triplex forming oligonucleotide can be administered to a cell *in combination with a separate DNA fragment*. The '376 patent also describes co-administration of a triplex forming oligonucleotide *with the recombination fragment*. Oligonucleotides were routinely chemically synthesized by commercial suppliers as of the priority date of the present application. If one of skill in the art wanted a TFO tethered to a donor nucleic acid, all one had to do was order its synthesis from a commercial supplier as was done in the present application (see page 17, lines 19-26). Clearly these molecules can also be synthesized separately. The '376 patent describes chemical synthesis of oligonucleotides at least at column 7, lines 34-58. Furthermore, methods for linking strands of DNA (e.g., generating a recombinant plasmid) were well known to one of ordinary skill in the art as of the priority date of the present application. It is clear that the concept of using TFOs tethered or untethered to a donor nucleic acid would be obvious to one of skill in the art based on the level of knowledge in the art and the disclosure provided in the '376 and '426 patents. Therefore, the present application is entitled to a priority date of 1995 and Chan is not prior art.

Based on what was known in the art concerning DNA fragments for use in homologous recombination methods, one of skill in the art could generate donor nucleic acids of any length, especially donor nucleic acids at least 30 nucleotides in length or between 10 and 40 nucleotides in length for use in the methods as defined by the claims of the present application (e.g., via chemical synthesis). As described above, and admitted by the Examiner in the Examiner's Answer (see page 20), the '376 and '426 patents describe the use of TFOs in conjunction with a donor nucleic acid to promote targeted recombination. Therefore, claims 12 and 25 are supported by the disclosure of the '376 and '426 patents.

(3) SUMMARY AND CONCLUSION

(1) The specification, in *combination* with information known in the art at the time of filing, clearly enables one skilled in the art to practice the claimed method. Appellant has demonstrated by virtue of the examples that the *in vitro* data is predictive of the *in vivo* results. Appellant has provided results for oligonucleotides linked or unlinked to a donor nucleic acid using both cell-free and cell systems. Absent some evidence otherwise, one skilled in the art would expect the oligonucleotides linked or unlinked to a donor nucleic acid to promote targeted recombination in animals as in the cell systems, based on the evidence in the specification.

(2) Appellant has extensively demonstrated that the claims of the present application are fully supported by the '376 and '426 patents. Therefore, Chan, published in 1999, is not prior art.

For the foregoing reasons, Appellant submits that claims 7-12 and 15-25 are patentable.

Respectfully submitted,

Patrea L. Pabst
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Date: February 23, 2006

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